Human neural stem cell-derived extracellular vesicles mitigate hallmarks of Alzheimer's disease.

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Public Summary:
Stem cell-based therapies to mitigate Alzheimer's disease (AD) neuropathology have shown very limited success, but small vesicles (EVs) derived from stem cells have shown considerable promise for the treatment of AD. In this study we used a mouse model of AD to show the regenerative potential of human neural stem cell-derived EVs on the cognitive impairments and inflammation found in the AD brain. AD mice received 1-2 intra-venous injections of hNSC-derived EVs. Later analysis of behavior 4-6 weeks later showed that the EV treatment improved memory and reduced anxiety in AD mice. the EV treatment also reduced amyloid-beta plaque accumulation and inflammation, both hallmarks of AD in those AD mice. Our results suggesting a novel therapy that could be developed to treat the AD brain and improve quality of life for AD patients.

Scientific Abstract:
BACKGROUND: Regenerative therapies to mitigate Alzheimer's disease (AD) neuropathology have shown very limited success. In the recent era, extracellular vesicles (EVs) derived from multipotent and pluripotent stem cells have shown considerable promise for the treatment of dementia and many neurodegenerative conditions. METHODS: Using the 5xFAD accelerated transgenic mouse model of AD, we now show the regenerative potential of human neural stem cell (hNSC)-derived EVs on the neurocognitive and neuropathologic hallmarks in the AD brain. Two- or 6-month-old 5xFAD mice received single or two intra-venous (retro-orbital vein, RO) injections of hNSC-derived EVs, respectively. RESULTS: RO treatment using hNSC-derived EVs restored fear extinction memory consolidation and reduced anxiety-related behaviors 4-6 weeks post-injection. EV treatment also significantly reduced dense core amyloid-beta plaque accumulation and microglial activation in both age groups. These results correlated with partial restoration of homeostatic levels of circulating pro-inflammatory cytokines in the AD mice. Importantly, EV treatment protected against synaptic loss in the AD brain that paralleled improved cognition. MiRNA analysis of the EV cargo revealed promising candidates targeting neuroinflammation and synaptic function. CONCLUSIONS: Collectively, these data demonstrate the neuroprotective effects of systemic administration of stem cell-derived EVs for remediation of behavioral and molecular AD neuropathologies.